Current Trends in Allergic Reactions:

A MULTIDISCIPLINARY APPROACH TO PATIENT MANAGEMENT

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TARGET AUDIENCE

Allergists/Immunologists, Pulmonologists, General Practitioners, Internists, Pediatricians, Psychiatrists, Allied Healthcare Professionals

STATEMENT OF NEED

Allergic diseases, including allergic rhinitis, latex allergy, food allergy, drug allergy, insect sting allergy, urticaria, and atopic dermatitis, affect a substantial proportion of the US population, and their incidence is increasing. Some of these reactions can be fatal if untreated or improperly treated, and the most common of all allergic reactions, allergic rhinitis, can contribute to more serious and difficult-to-treat conditions such as otitis media, sinusitis, and asthma. Despite their rising frequency and potentially serious consequences, allergic disorders are commonly unrecognized, and even the cases that are correctly diagnosed are often suboptimally treated. These facts underscore the need for comprehensive contemporary educational activities for healthcare professionals in the identification and management of allergies. This mandate is supported by consultation with leading experts in allergic disease, a review of the current literature, and the results of surveys conducted at prior symposia.

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Current Trends in Allergic Reactions: A Multidisciplinary Approach to Patient Management

Highlights From a Conference Held February 10-11, 2003 in Bethesda, Maryland

List of Abbreviations

AR	Allergic rhinitis
Ig	Immunoglobulin
H_1	Histamine type 1
H_2	Histamine type 2
QOL	Quality of life

INTRODUCTION

Allergy is defined as the acquired potential to develop immunologically mediated reactions to allergens (substances that are normally innocuous, such as pollen, mold spores, animal dander, dust mites, foods, insect venom, and drugs). Although the term "allergy" is often used to describe any type of immunologic reactivity, it refers in its strict sense only to the clinical expression of atopic disease mediated by immunoglobulin E (IgE) antibodies.[1] In this newsletter, the term is used primarily to designate IgE-mediated reactivity. However, in discussions of food allergy, latex allergy, and drug allergy, the term "allergy" is used to refer to all immune reactivity, not just IgE reactivity.

The prevalence of allergic diseases in the United States is high, and it continues to increase each year. All allergic conditions cause significant discomfort and impair quality of life, and some have potentially serious or fatal consequences as well. Yet the impact of these disorders on patients' lives is very often underestimated, and there are many barriers to optimal management. These range from the difficulties of identifying and avoiding culprit allergens to the challenges of designing an effective, well-tolerated treatment regimen that patients can accept and adhere to over the course of many years. Fortunately, the broad range of therapies available today make it possible to manage these conditions safely and effectively in the vast majority of cases.

Acknowledging the importance of allergic disorders in the clinical practices of healthcare professionals across many disciplines, a group of allergists, primary care physicians, otolaryngologist, immunologists, nurse practitioner, physician assistant, and pharmacist attended a conference presented by the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, on February 10 and 11, 2003, to discuss current understanding of the etiology, diagnosis, prevention, and management of allergic rhinitis (AR); allergies to latex, foods, drugs, and insect stings; urticaria; and atopic dermatitis. Atopy is defined as a tendency to develop asthma, AR, and/or atopic dermatitis, and to develop allergies because of a genetically acquired hyperresponsiveness to allergens. Thus, atopic individuals have a substantially increased likelihood of producing IgE antibodies to food allergens and aeroallergens. Although asthma is within the spectrum of atopic diseases and is clearly linked to allergy, it is such a large and complex topic that in-depth coverage of it was beyond the scope of the conference. This publication presents a synopsis of the clinical highlights from this event.

OVERVIEW OF ALLERGIC DISEASES

Epidemiology

The prevalence of allergic diseases such as AR and atopic dermatitis has risen substantially in recent decades.[2,3] AR alone is believed to affect almost 40 million Americans, including 20% of all adults and up to 40% of children.[4-6] The costs associated with allergic disease are extraordinarily high: one analysis estimated it at $7.9 billion per year, of which $4.5 billion was spent on direct care and $3.4 billion on indirect costs, related primarily to lost work productivity.[4]

Educational Objectives

After reading this newsletter, clinicians should be able to:

- Discuss the increasing prevalence of allergic diseases and their impact on patient quality of life
- Describe the pathophysiology of allergic reactions
- Compare and contrast different types of allergic reactions and their presentation, diagnosis, and treatment
- Evaluate treatment options in the management of allergic reactions
- Consider clinical implications of allergic reactions and treatment on patient care, function, quality of life, and adherence

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Impact on Productivity

Of all the allergic disorders, AR probably has the greatest impact on productivity, because it tends to be a lifelong condition, because the causative allergens are usually difficult or impossible to avoid, and because of its pathophysiologic relationship to asthma. Although AR often begins in childhood, its highest prevalence is between the ages of 18 and 49—the peak career-building, child-rearing years.[7] In addition to millions of days of workplace absence each year, AR causes about 28 million days of restricted work activity.[8] The side effects of some allergy therapies can detract even further from workplace performance: one study of decreased productivity related to the sedating effects of traditional (or first-generation) antihistamines estimated the costs at $4 billion per year.[9]

AR also affects classroom productivity and functioning in children, chiefly because of school absences. In fact, AR and asthma are the 2 leading causes of absenteeism due to chronic illness.[10] On any given day, 10,000 American children miss school because of AR, for an annual total of 2 million lost school days.[8] Even when they are in school, children with AR often have trouble concentrating or even staying awake because of the symptoms themselves and because of treatment-related drowsiness. In a study comparing children without allergies, children with inactive allergies, and children with active AR, the latter group was found to have poorer short-term memory, impaired ability to acquire knowledge, reduced ability to apply knowledge, and shortened attention span.[10] In another study, children with AR performed significantly worse academically than did nonallergic children. Treatment with one of the newer (or second-generation) nonsedating antihistamines elevated their performance to nearly that of nonallergic children, whereas treatment with a first-generation antihistamine worsened their performance even further.[11] While some evidence shows that first-generation agents impair scholastic performance and second-generation agents do not,[12] one trial by Bender and colleagues found no differences between placebo, a first-generation antihistamine, and a second-generation antihistamine in learning ability, reaction time, or self-reported somnolence in children with a history of seasonal AR.[13]

Urticaria is also associated with reduced productivity. For example, a study of 170 consecutive patients with various forms of urticaria found that 50% of those with delayed-pressure urticaria and 26% of those with chronic idiopathic urticaria had taken time off from work during the preceding week because of their condition.[14]

Impact on Quality of Life

Like productivity, quality of life (QOL) is affected adversely by allergic disease.[15,16] In a cross-sectional study comparing QOL in 111 adults with AR and 116 control subjects, those with AR had lower scores on all of the 9 domains measured, including social functioning, role limitations, mental health, energy/fatigue, and pain; the difference was highly significant ($P<.0001$) in 8 of the 9 domains.[17] In a separate study of 142 patients with chronic urticaria, QOL scores were almost identical to those of patients with coronary heart disease in terms of low energy levels, feelings of social isolation, and emotional distress.[18]

Allergies also affect QOL for younger patients. In a study of 18 adolescents, those with AR reported difficulty concentrating and doing schoolwork, feeling tired and worn out, accomplishing less than their peers, and feeling irritable and generally unwell.[16] Because of the discomfort caused by their symptoms, children and adolescents with allergies may be more likely than their nonallergic peers to be unresponsive, apathetic, irritable, and uninterested in activities. These behaviors are so common in allergic children that the term "allergic irritability" has been coined to describe them.[10]

The QOL deficits caused by allergic disease can be alleviated or worsened by treatment, depending on the choice of therapy. For example, a number of studies have concluded that the adverse effects of first-generation antihistamines worsen QOL for patients with AR, whereas second-generation antihistamines and intranasal corticosteroids significantly improve it.[19-21] Similarly, second-generation antihistamines enhance QOL for patients with chronic urticaria.[22]

PATHOPHYSIOLOGY OF ALLERGIC REACTIONS

In atopic individuals, exposure to an antigen (allergen) sets off an immune-mediated cascade of inflammatory events that result in the classic symptoms of allergic disease. The process begins with the first exposure to the antigen, which is broken down into smaller peptides by antigen-presenting cells. The peptides are presented to T cells, which secrete cytokines that induce B cells to produce antigen-specific (Ig)E. These IgE molecules then bind to high-affinity FcεRI receptors on basophils and/or mast cells (Figure 1). This step is described as sensitization.[23]

When a sensitized individual next encounters the same allergen, the allergen cross-links the IgE molecules bound to mast cells and basophils, activating them and causing them to release inflammatory mediators such as histamine,

prostaglandins, and leukotrienes[24] (Figure 1).This step, called the immediate hypersensitivity or early-phase reaction, occurs within minutes of re-exposure to the allergen.[23] Histamine is the most well studied of these mediators: its activation of the H_1 class of histamine receptors causes certain smooth muscles to contract, stimulates sensory nerves, and increases mucus secretion and vascular permeability, resulting in fluid leakage and tissue edema[25] (Table 1, page 4). This pathophysiologic reaction is the same regardless of the type of allergy; the clinical symptoms are determined by the nature of the allergen and the site of its effect. With an inhaled allergen, the affected site is the upper airway, and the response manifests as sneezing, nasal itching, congestion, and rhinorrhea.[23] With an ingested allergen, the affected site is the gut, and the response manifests as bloating, cramping, nausea, vomiting, and diarrhea.[26]

Many patients also have a late-phase reaction, which generally begins 2 to 6 hours (even later in some patients) after allergen exposure and is often more severe and prolonged than the immediate-phase reaction. During this phase, cytokine and chemokine gene induction leads to the accumulation of inflammatory leukocytes, including neutrophils, basophils, eosinophils, and T cells. The consequences are inflammation, swelling, mucus hypersecretion, and airway hyperresponsiveness. This phase can persist for up to 24 hours before receding.[23]

As noted above, allergic reactions are strictly defined only as those mediated by IgE. However, certain disorders such as allergic contact dermatitis are loosely described as allergic reactions even though they are mediated by T cells and other pathways. A single allergic disease may involve more than one immunologic mechanism.

ALLERGIC RHINITIS

Description and Diagnosis

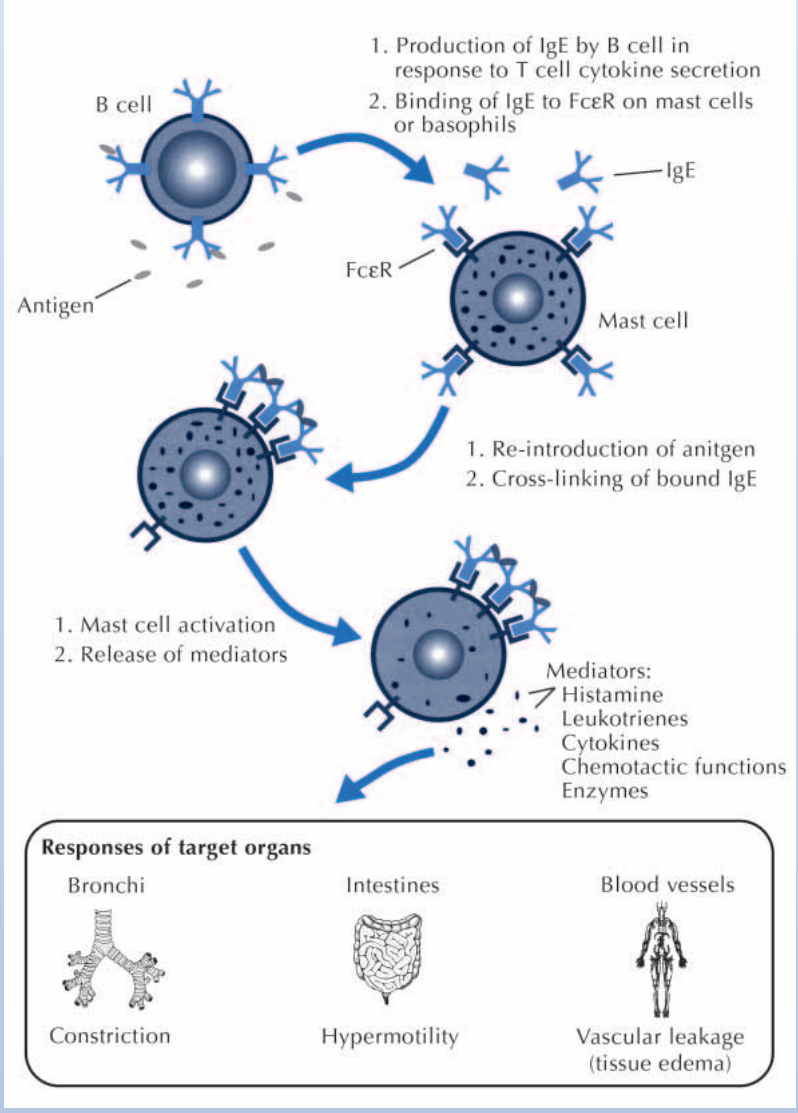
AR is an IgE-mediated reaction of the nasal mucosa in which the effects of histamine and other mediators on sensory nerves cause sneezing and itching, and the effects on vascular permeability and mucus secretion result in congestion and rhinorrhea.[23] Repeated allergen exposure makes the nasal mucosa hypersensitive, so symptoms occur not only in response to low levels of allergen but also to nonspecific irritants such as tobacco smoke and perfume.[19,25]

Diagnosis of allergy rests primarily on the medical history and physical examination; in most cases, the results of skin and serologic testing merely confirm the clinician's suspicions and are used mainly to identify unsuspected allergens and guide the approach to immunotherapy if indicated. The allergens most often implicated in seasonal AR are grass, tree, and weed pollens and fungal spores,[24] and those implicated in perennial AR are usually house-dust mites, animal dander, mold, and cockroach allergens.[27] Seasonal (intermittent) AR is characterized by watery rhinorrhea; repetitive sneezing; pruritus of the eyes, ears, nose, and throat; watery eyes; and nasal congestion. Perennial (persistent) AR has similar symptoms but is occasionally associated with more severe nasal congestion. Many patients have perennial AR with seasonal exacerbations, and in areas of the country in which climate and flora change minimally from season to season, there is little meaningful difference between seasonal and perennial disease.[24]

A thorough evaluation of AR includes checking for the presence of common comorbidities such as asthma, sinusitis, and otitis media. Growing evidence

FIGURE 1

Sensitization and the Immediate Hypersensitivity Reaction



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suggests that these conditions co-occur so often because AR plays a causative role. For example, intranasal challenge with relevant allergens in adult humans with AR and in sensitized monkeys produces classic AR symptoms along with eustachian tube dysfunction; by contrast, these symptoms are not produced by challenging subjects with nonallergic rhinitis.[28] For patients with both AR and asthma, treating the allergies with oral antihistamines or topical steroids improves pulmonary function and airway symptoms as well. However, treatment of asthma usually requires therapy beyond treatment of the associated AR.[29]

Conjunctivitis is a common feature of allergic disease, although it also can be caused by infections or hormonal changes. The most common complaint of patients with allergic rhinoconjunctivitis is watery or itchy eyes; ocular symptoms such as redness, soreness, stinging, or swelling also occur albeit less frequently.[16] In contrast, ocular pain and photophobia generally point to other diagnoses. Redness of the eyes can be a sign of allergy, or it may indicate conjunctivitis, corneal disorders, acute glaucoma, or acute uveitis.

Prevention and Treatment

As with all types of allergic disease, management of AR has 4 key components: allergen avoidance, systemic pharmacotherapy, topical pharmacotherapy, and immunotherapy. Proactive patient education and regular reinforcement are the foundation of each of these components. Patients and their families should be given written and verbal instructions on avoidance measures, when and how to use their medications, and what circumstances warrant an office or emergency room visit. For children with severe or life-threatening allergies, education should be extended to all caregivers, including school personnel. The American Academy of Asthma, Allergy and Immunology has a library of patient-centered publications available at http://www.aaaai.org/patients.stm, and other valuable consumer information may be obtained from the Food Allergy & Anaphylaxis Network (http://www.foodallergy.org), the Allergy & Asthma Network Mothers of Asthmatics (http://www.aanma.org), and Lung Line® Information Service (http://www.nationaljewish.org).

Allergen avoidance is a crucial step in allergy management and in reducing the need for pharmacologic intervention. Although it is very difficult to avoid completely the pollens, molds, and dust mites that cause most cases of respiratory allergy, conscientious use of environmental control measures can reduce allergen exposure considerably and should be recommended whenever feasible (Table 2).

Recent evidence suggests that primary prevention may be possible in infants who are at risk of developing allergies and asthma. For example, one study followed the infants of 291 couples in which both parents were atopic. The families were prenatally randomized into 2 groups: One implemented environmental measures to reduce prenatal and postnatal allergen exposure, and the other received no intervention. By 1 year of age, respiratory symptoms such as wheezing and use of medication for wheezing were significantly less common in the allergen-avoidance group than in the control group.[30] Other evidence suggests that primary prevention of food allergies may be achieved by the mother's avoiding allergenic foods while breast-feeding and by delaying the introduction of solid foods to the child.[31] Similarly, avoidance of food allergens and dust mites in infancy has been shown to significantly reduce the incidence of allergy and eczema at the age of 2 years in high-risk children.[32] In one study, treating pregnant women and subsequently their infants with cultures of *Lactobacillus* GG halved the incidence of atopic eczema in the children compared with placebo-treated children.[33] However, these types of trials are in their early stages, and more information is needed before there is general implementation of the approaches that have been evaluated.

Systemic Pharmacotherapy

Management of AR is based on the severity of symptoms and their impact on comorbidities and QOL. A stepwise approach to drug therapy is outlined in Figure 2, page 6.

Table 1

Common Symptoms of Allergic Rhinitis and Their Mediators

	Mediators				
Symptoms	**Histamine**	**Prostaglandins**	**Leukotrienes**	**Bradykinin**	**PAF**
Tickling	X	X			
Itching	X	X			
Nose rubbing	X	X			
Allergic "salute"	X	X			
Sneezing	X		X		
Nasal congestion	X		X	X	X
Stuffy nose	X		X	X	X
Mouth breathing	X		X	X	X
Snoring	X		X	X	X
Runny nose	X		X		
Postnasal drip	X		X		
Throat clearing	X		X		

PAF = platelet-activating factor.

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Antihistamines

Oral antihistamines have long been the mainstay of drug treatment for AR. By antagonizing H_1 receptors, they rapidly and significantly control sneezing, pruritus, and rhinorrhea, as well as alleviating related symptoms in the eyes and throat. Some members of this class improve nasal congestion, but their impact on this component is relatively modest.[6]

First-generation oral antihistamines are generally lipophilic and hence can cause psychomotor and cognitive impairment because of their ability to penetrate the blood-brain barrier and their antiserotonin and anticholinergic effects.[6] By comparison, the newer, or second-generation antihistamines cause little or no sedation due to their low lipophilicity, their large molecular size, their greater affinity for peripheral H_1 receptors, and their relative lack of affinity for neuroreceptors.[34]

All second-generation agents are preferable to their predecessors, but there may be differences even within this class in terms of sedative and cardiotoxic effects, as well as efficacy and onset of action. For example, some may cause sedation at standard or higher-than-standard doses (such as those used by patients with refractory AR or other allergic conditions such as urticaria).[35] In objective tests, only fexofenadine and ebastine (a terfenadine derivative not yet available in the United States) have been shown to be virtually without sedative or performance-impairing effects, regardless of dose.[34]

The onset of action of oral antihistamines is generally rapid. Fexofenadine and cetirizine begin to relieve symptoms within an hour of administration, and loratadine has a somewhat later onset of action at approximately 3 hours.[35,36] In general, better therapeutic results are achieved when antihistamines are taken routinely rather than sporadically. Many of the second-generation antihistamines are available in combination with a decongestant, which may be helpful for patients with pronounced nasal congestion and blockage.[6]

Decongestants

Decongestants are sympathomimetic agents that alleviate nasal blockage. Their potential side effects include hypertension, restlessness, agitation, tremor, headache, insomnia, urinary obstruction, and changes in cardiac rhythm.[6] One of the 2 commonly used oral decongestants, phenylpropanolamine, was recently deemed unsafe by the Food and Drug Administration.[37] The other, pseudoephedrine, remains available. Products containing phenylpropanolamine are no longer sold in stores, but patients may still have them at home and should be advised to discard them.

Leukotriene Modifiers

Several agents have been developed for controlling allergic symptoms by inhibiting the synthesis of leukotrienes (eg, zileuton) or blocking their receptors (eg, montelukast, zafirlukast). These agents are modestly effective for patients with asthma and less so in AR, and they are not currently seen as a substitute for corticosteroids. They help control exercise-induced asthma and often permit a decrease in the dose of inhaled corticosteroids.[38,39] According to a recent comprehensive literature review, leukotriene receptor antagonists are not superior to second-generation antihistamines in terms of relieving congestion or other nasal symptoms. The author concluded that leukotriene receptor antagonists do not have a unique role in the treatment of AR, whether or not it is accompanied by asthma.[40]

Oral Corticosteroids

Systemic corticosteroids are highly effective anti-inflammatory agents and may be necessary for patients with severe symptoms, or to gain control of symptom exacerbations.[5] However, they have a number of potentially serious side effects, such as

Table 2

Environmental Control of Allergen Exposure

Allergen	Recommendations for Reducing Exposure
Animal dander	• Remove animal from house, or, at minimum, keep animal out of patient's bedroom • Seal (or cover with a filter) air ducts that lead to bedroom • Install room air filters (HEPA-type)
Dust mites	*Essential:* • Reduce indoor humidity to <50% • Encase mattress, pillow, and box springs in an allergen-impermeable cover • Washing bedding weekly in hot water (≥130°F) *Desirable:* • Minimize upholstered furniture • Remove carpets from the bedroom and from other rooms where they are laid on concrete
Cockroaches	• Do not leave food or garbage exposed • Use poison bait or traps
Pollens and outdoor molds	• Use air conditioning • Limit exposure during season by staying indoors with windows closed, especially when pollen levels are elevated
Indoor mold	• Reduce indoor humidity to <50% • Fix all water leaks • Clean moldy surfaces

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osteoporosis, glaucoma, and growth retardation in children. For this reason, topical steroids are preferred for the treatment of ongoing allergy, and courses of oral steroids should be kept to a maximum of 3 to 7 days.[25]

Topical Pharmacotherapy

Intranasal Corticosteroids

Highly potent, rapidly metabolized intranasal steroid sprays such as beclomethasone dipropionate, flunisolide, triamcinolone acetonide, budesonide, fluticasone propionate, and mometasone furoate are the most effective agents currently available for preventing itching, sneezing, rhinorrhea, congestion, and cough. These agents act by reducing inflammatory cell infiltration, decreasing vascular permeability, diminishing the response of mucous glands to cholinergic stimulation, and controlling nasal hyperreactivity.[6,41]

Nasal steroids require more time than do oral antihistamines to become effective and to exert maximum benefit; instead of the 1- to 3-hour onset of action of most antihistamines, nasal steroids may take 4 to 12 hours to provide symptom relief, with maximum benefit usually occurring within 2 weeks. Many patients require a combination of a nasal steroid and an antihistamine for maximum symptom relief. Patients should be instructed to use topical steroids on a regular basis, even when symptoms are not present.[25]

Although none of the topical steroids have a dramatic effect on growth velocity in children, there may be some modest differences within the class. For example, a year-long study of 98 prepubertal children with perennial AR showed that mometasone 100 mcg/day had no effect on growth,[42] whereas a separate year-long study of 100 children found that beclomethasone 336 mcg/day significantly slowed growth compared with placebo ($P<.01$).[43] Two-week courses of intranasal triamcinolone or fluticasone had no effect on lower-leg growth in a recent study using knemometry, which is a highly sensitive measure of short-term changes in the distance between the knee and the heel.[44] All the newer agents are effective and safe; the distinction between them is primarily one of patient preference for certain sensory attributes (including overall comfort, burning, run-off, taste, and odor). Since patient preference can influence adherence, this aspect should be considered in prescribing.

Topical Antihistamines

Azelastine is a second-generation antihistamine nasal spray that can significantly decrease allergen-induced sneezing, rhinorrhea, itching, and nasal congestion in patients with seasonal AR.[45] In a head-to-head comparison, it was found to be equivalent or superior to cetirizine in patients with seasonal AR, as well as being significantly less likely to cause drowsiness.[46]

Mast Cell Stabilizers

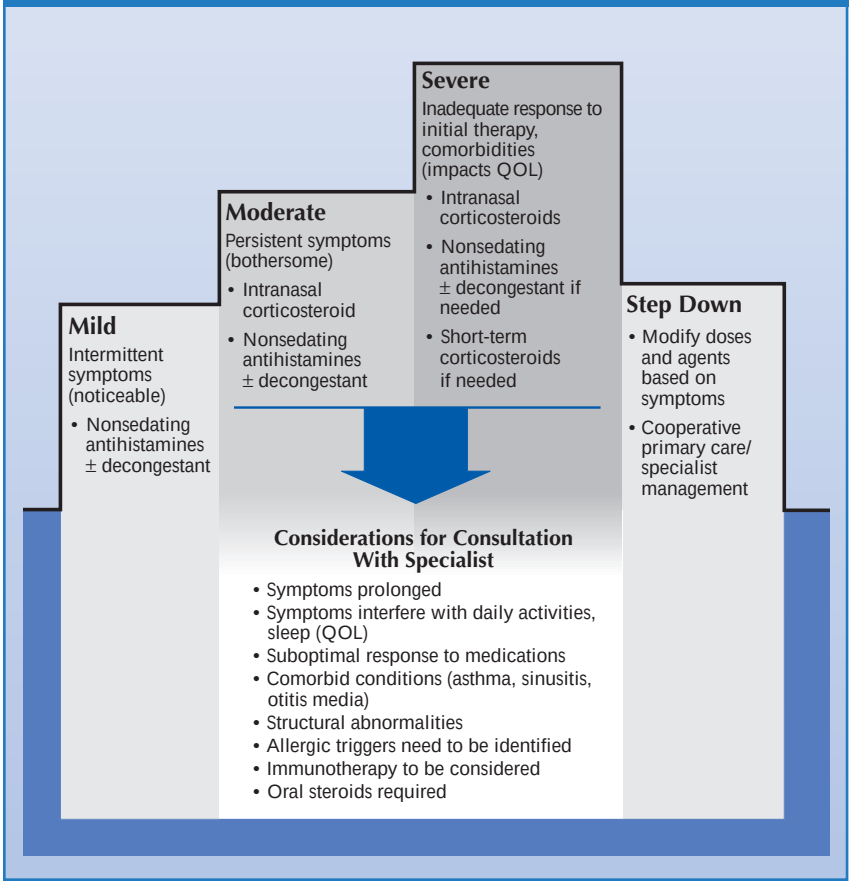
Mast cell stabilizers, which include intranasal cromolyn sodium and cromolyn-like agents, act by stabilizing the membranes of mast cells, thereby inhibiting the release of histamine and other inflammatory mediators such as prostaglandins and leukotrienes. Modulation of cytokine release also reduces eosinophil and neutrophil counts during the late-phase response. In addition, mast cell stabilizers may suppress the activity of sensory nerve endings. Together, these activities help alleviate both the early- and late-phase symptoms of AR.[25] Cromolyn can be used therapeutically or, preferably, prophylactically in chronic AR to reduce the symptoms of sneezing, itching, and rhinorrhea, although it is less effective against nasal congestion. Many patients do not have adequate responses to cromolyn. An advantage of mast cell stabilizers is their excellent safety record. Disadvantages include a very short duration of action, which requires administration several times per day,[41] and poorer efficacy than that of either second-generation oral antihistamines or nasal steroids.[25] Adherence to a regimen of multiple daily doses may be poor, so the recommended number of daily doses should be adjusted downward as symptoms abate.

Intranasal Decongestants

Intranasal decongestants are available over the counter and are generally more effective than oral ones, although their benefits are limited to

FIGURE 2

A Stepwise Approach to Drug Therapy for AR



congestion. A major and often underestimated side effect of these agents is rhinitis medicamentosa, a rebound phenomenon that results in a marked exacerbation of nasal congestion when the agents are used for more than 3 days.[24] Treatment of rhinitis medicamentosa requires complete discontinuation of nasal decongestants, which patients may find very difficult, and possible addition of steroids.[41]

Topical Anticholinergics

Rhinorrhea can be safely and effectively alleviated by intranasal anticholinergic agents such as ipratropium bromide.[47] In a study of 533 patients with allergic or nonallergic perennial rhinitis, both ipratropium nasal spray and beclomethasone dipropionate nasal spray were superior to placebo in reducing the severity and duration of rhinorrhea, and the combination of the 2 sprays was more effective than either one alone.[48]

Immunotherapy

Immunotherapy consists of repeated subcutaneous injection of potent standardized extracts of specific allergens. Its efficacy in the treatment of AR (particularly if caused by pollen, mold spores, dust mites, or animal dander) is variable, and it is even more so in allergic conjunctivitis and allergic asthma. Its major benefit is that if it is clinically effective, it may allow a reduction in pharmacotherapy. Its mechanism of action remains unclear.[26] It has recently become apparent that when immunotherapy is successful, it can confer long-term protection even after injections are discontinued.[49] A recent multicenter study of 205 children with grass and tree allergies found that active treatment may provide some protection against the onset of asthma when measured after 3 years of therapy.[50]

Immunotherapy is generally considered for patients with limited allergies that markedly affect QOL or daily function and who do not attain adequate symptom relief with drug therapy.[6] The course of therapy usually begins with 1 to 2 injections per week for up to 1 year, followed by once-monthly injections for at least 3 to 5 years (or longer for some patients). Because anaphylactic reactions can occur during immunotherapy, immunotherapy must be administered by trained professionals in a facility with direct access to emergency treatment.[26] The risks of systemic reactions and anaphylaxis are major limitations to the use of immunotherapy, especially for patients with asthma and those using beta-adrenergic therapy.

LATEX ALLERGY

Description and Diagnosis

Latex allergy is an immune response to the proteins in natural latex rubber. It has become an increasingly important concern, particularly in the healthcare environment. Before the advent of universal blood and body fluid precautions in 1987, reports of allergic asthmatic reactions to natural rubber latex protein were relatively uncommon, but they rose dramatically from the late 1980s through the mid-1990s. The simplest and most compelling explanation is the profound increase in the use of latex gloves. Between 1985 and 1992, latex glove demand in the United States rose from approximately 2 billion to almost 8 billion.[51] During the early 1990s, the prevalence of latex allergies was about 17% among exposed US healthcare workers[51] and as high as 51% among children with spina bifida (who undergo numerous surgical procedures).[52] Other individuals at high risk for latex allergy include those with urogenital conditions, eczema, or a history of multiple surgeries; those who work in the rubber industry; those who work in other occupations that require latex gloves; and those who must use catheters. The potential routes of latex exposure are numerous and include contact with skin (gloves, tourniquets, compression bandages, or blood pressure cuffs), contact with mucous membranes (condoms, medical gloves, or the rubber tips of enema applicators), inhalation (airborne powder containing latex particles from gloves), and intravascular contact (intravenous injection ports).[51]

The most common reactions to latex are actually nonallergic (irritant) reactions, usually in the form of mild contact dermatitis. Contact dermatitis may also be mediated via T cells, but individuals with this condition can later go on to develop IgE-mediated latex allergy. Some reactions to latex are classic responses mediated by IgE, causing immediate symptoms in the skin, eyes, nose, and lungs and systemic manifestations such as life-threatening hypotension, tachycardia, and shock. Other latex allergies are mediated by T cells and tend to appear hours or days after exposure; most signs and symptoms are confined to the skin. Patients with latex allergy are at risk for cross-reactivity to avocado, banana, chestnut, and passion fruit, among other foods,[51] because of the significant sequence homologies between antigenic epitopes of latex proteins and certain plants and fruits. Skin and in vitro tests for latex allergy may be negative despite a clear clinical history; such patients should be considered at risk for future reactions.[53]

Prevention and Treatment

Because latex allergy has the potential to induce life-threatening anaphylaxis with repeated exposure, avoidance is of the utmost importance. Patients can avoid most exposures if they are informed and vigilant, but they should be instructed to carry self-injectable epinephrine at all times in case of unanticipated encounters. Education on how to use epinephrine kits should begin with the first prescription and then be reinforced regularly, and at least one office staff member should be proficient in providing such instruction.[53] In healthcare settings, switching from powdered high-protein latex gloves to nonpowdered (or light-powdered) low-protein natural rubber latex gloves may reduce the aerosolized latex protein powder load, and using gloves made of alternative materials can reduce cutaneous exposure.[51]

FOOD ALLERGY

Description and Diagnosis

Another potentially life-threatening reaction is food allergy, a group of disorders in which an immunologic hyperreactivity response follows ingestion of particular food proteins despite the digestive tract's protective physiologic and immunologic barrier to ingested antigens. These are distinct from nonimmunologic food reactions. In fact, not all immunologic reactions to foods are IgE mediated (celiac disease, for example), but those that are IgE mediated are associated with the risk of anaphylaxis, and they are the ones generally referred to as "food allergies."

About 90% of food allergies in children are caused by milk, eggs, peanuts, wheat, soy, and tree nuts, whereas usually food allergies in adults are provoked by peanuts, tree nuts, fish, and shellfish. Food allergies are most prevalent during the first few years of life and tend to decline with time, except for nut, fish, and shellfish allergies.[53]

Signs and symptoms of immune-mediated food reactions may occur within minutes to a few hours of ingestion of the offending food; even if symptoms subside, they may recur hours later. Localized manifestations include itching or tingling of the lips, palate, tongue, or throat; swelling of the lips or tongue; hoarseness and tightness of the throat; nausea or vomiting; cramps; and diarrhea. Systemic symptoms such as hypotension and loss of consciousness may occur also, as may urticaria, flushing, and other skin symptoms; chest tightness, wheezing, and shortness of breath; and upper respiratory symptoms similar to those of AR, including nasal congestion, sneezing, rhinorrhea, and ocular itching and tearing. Oral allergy syndrome—a mild localized manifestation to certain fresh fruits and vegetables that is often seen in patients with seasonal AR—is IgE mediated, but is limited to local reactions. It is harmless and self-limiting, whereas systemic food allergy is potentially life-threatening and requires immediate treatment.[53]

Prevention and Treatment

As with latex allergies, reactions to foods can be minimized by careful avoidance measures, but accidental exposures are not uncommon. Patients should be taught to read food labels and to refrain from eating any food containing unknown ingredients. If culprit foods are eaten accidentally, oral antihistamines can be used to manage mild reactions such as localized dermatologic or gastrointestinal symptoms. Severe reactions, which can include anaphylaxis, must be treated initially with subcutaneous or intramuscular epinephrine; should the patient not respond to this adequately, intravenous epinephrine should be considered. Many patients have a delayed or biphasic reaction that may be very severe, so extended observation is required in all cases.[53] There are no reliable data on the clinical efficacy of immunotherapy for food allergy, and it is associated with a high risk of systemic reactions. It is therefore not recommended.

DRUG ALLERGY

Description and Diagnosis

Allergic drug reactions, which account for approximately 5% of all hospital admissions and occur in up to 20% of hospitalized patients, are complex clinical entities, because they can be caused by a range of drug classes, present with a wide variety of signs and symptoms, and affect virtually any organ system.[53,54] Some drug reactions are mediated by IgE, and manifest as urticaria, pruritus, and/or angioedema, and may be as severe as anaphylaxis with hypotension. Other reactions involve the interaction of complement and IgG or IgM with cell-bound drug antigens; the resulting cell destruction can present as immune hemolytic anemia, thrombocytopenia, or granulocytopenia. Other types of drug allergies include immune-complex reactions, in which drug molecules covalently bound to proteins form complexes with antibodies, causing serum sickness or lupus syndromes. Alternatively, drug reactions may be mediated by lymphocytes; these inflammatory reactions may manifest as contact dermatitis or morbilliform rashes. Penicillin and other antibiotics, quinidine, sulfonamides, methyldopa, and polypeptide hormones are among the many products that may provoke immunologic drug reactions.[53,54]

Prevention and Treatment

Patients who have experienced allergic drug reactions should be instructed to memorize the generic and trade names of the offending agents and advise all caregivers of their allergy. For immediate severe drug reactions, treatment consists of discontinuing the offending agent, administering epinephrine, and prescribing a second-generation antihistamine to help control urticaria, angioedema, and pruritus. Oral corticosteroids may also be indicated. In rare circumstances, it may be necessary to "treat through" an allergic reaction—that is, to continue the drug despite the reaction. However, this can be highly dangerous and is used only as a last resort. In such cases, pretreatment with antihistamines and corticosteroids is used to suppress the reaction. Because of the potential risks, which include progression of skin rash to Stevens-Johnson syndrome and involvement of vital organs and anaphylaxis, consultation with an allergy/immunology specialist is recommended for these patients.[53]

INSECT STING ALLERGY

Description and Diagnosis

Though insect bites may cause localized allergic swelling, they seldom cause systemic reactions. Systemic allergic reactions are caused mainly by stinging insects of the Hymenoptera order, such as honeybees, yellow jackets, hornets, wasps, and fire ants. These reactions are mainly cutaneous—involving extensive swelling, itching, and erythema originating from the sting site and lasting for several days—but they can be systemic, triggering

anaphylaxis, with generalized cutaneous symptoms distant from the sting site, and potentially life-threatening cardiovascular and respiratory symptoms.[55] Other than a history of systemic reaction, there are no criteria to identify those at risk for insect-sting anaphylaxis. In more than 20% of anaphylactic episodes, there is a biphasic reaction, with a late-phase response occurring 3 to 6 hours after the sting. These late-phase responses can be particularly severe and difficult to treat; patients who experience anaphylaxis should therefore be kept under surveillance for several hours after a sting.[26]

Prevention and Treatment

Like airborne allergens, insect stings are difficult to avoid completely. Common-sense measures include wearing long pants and long-sleeve shirts outdoors and not wearing brightly colored or flowered clothing, perfume, or hairspray. When stings occur despite efforts at avoidance, the stinger should be removed by flicking or scraping as soon after the sting as possible.[55] Application of cold compresses and administration of analgesics for pain may be all that is required for immediate local reaction; for more severe reactions, oral nonsedating antihistamines are recommended.[55] If the swelling is extensive or painful, a 3- to 7-day course of oral steroids is recommended, preferably beginning within 2 hours of the sting. In cases of anaphylaxis, subcutaneous or intramuscular administration of epinephrine is indicated. Corticosteroids may also be used to prevent late- or second-phase anaphylaxis.[56] Venom immunotherapy is a very effective form of treatment for individuals at risk for anaphylaxis: fewer than 3% of patients have further episodes.[55] Patients 16 years old or younger who have experienced cutaneous reactions without other manifestations generally do not require immunotherapy, since they have only a 10% chance of experiencing a systemic reaction if re-stung.[55]

URTICARIA

Description and Diagnosis

Urticaria is a common condition characterized by intensely pruritic, erythematous, elevated skin lesions.[14] In most cases, urticaria can be characterized as either acute or chronic. Acute urticaria, which affects up to 20% of individuals at some time in their lives, is self-limited. Many cases are reactions to foods or drugs. Chronic urticaria is diagnosed when the condition persists beyond 6 weeks[18]; 50% of patients have symptoms for more than 6 months, and 20% have them for 10 or more years, although individual urticarial lesions, whether of acute or chronic urticaria, are characteristically short-lived, generally abating within 24 hours. In the majority of cases, an etiologic factor cannot be identified. Urticaria may also be induced by pressure, cold, heat, exercise, or sun exposure. Some patients with urticaria may have underlying diseases such as systemic lupus erythematosus, malignancies, or thyroid disease.[53]

Angioedema is caused by a similar edematous process to urticaria but extends below the dermis.[53] The differential diagnosis includes cellulitis, edematous states, trauma such as insect stings, and fasciitis; these can usually be ruled out on the basis of the history. The patient should be asked whether the symptoms were accompanied by urticaria, pruritus, and/or gastrointestinal symptoms, whether they were related to medication use (beta-lactam antibiotics in particular), and whether any other triggers were apparent. The symptoms tend to occur about 30 minutes after contact with the antigen. Angiodema may be IgE mediated but like urticaria, is more often idiopathic. When the reaction is IgE mediated, it is often observed in atopic patients, and it may include anaphylaxis.

Prevention and Treatment

In cases in which the triggers of chronic urticaria can be identified, patients should do their best to stay away from them and minimize modulating factors such as alcohol, exertion, and stress. Nonsedating H_1 antihistamines are the treatment of choice and are generally effective in relieving pruritus and lesions. When necessary, H_2 antagonists, tricyclic antidepressants such as doxepin, or leukotriene modifiers can be added to the H_1 antihistamine regimen (although the role of the latter agents is not yet well defined). An every-other-day oral steroid regimen can be added if the foregoing agents are not sufficiently effective, but the dosage should be tapered as soon as the symptoms are controlled.[53]

ATOPIC DERMATITIS

Description and Diagnosis

Atopic dermatitis is a chronic, relapsing, highly pruritic inflammatory skin disease that typically involves the flexural areas of the knees, elbows, ankles, and neck in adults and the face and outer limbs in children.[57] Although it can affect patients of any age, its onset is usually very early; in fact, it is the most common chronic skin disease among young children. Like other atopic diseases, atopic dermatitis is increasing in prevalence: epidemiologic studies suggest that it has doubled or tripled since the 1960s, and it is now seen in about 17% of American children.[57,58] The intense itching, skin excoriations, and secondary infections profoundly diminish QOL, disrupt sleep, and impair psychosocial adjustment.[58]

Although much remains to be learned about the pathophysiology of atopic dermatitis, it is clearly associated with dysregulation of numerous inflammatory cytokines, mediators, and T cells. The allergic nature of the disease is further supported by elevations in IgE level[59] and a strong epidemiologic relationship to other atopic conditions: almost 80% of children with atopic dermatitis go on to develop AR or asthma.[60] Triggers of atopic dermatitis can include foods, aeroallergens such as dust mites, toxins secreted by *Staphylococcus aureus*, and possibly even autoantigens.[60]

Prevention and Treatment

In addition to avoiding common skin irritants, food allergens, and airborne allergens, patients with atopic dermatitis should practice palliative skin care, which includes hydrating the skin with emollients, avoiding irritating fabrics and laundry products, and taking daily soaking baths. Topical steroids are considered first-line treatment for atopic dermatitis, but they are not indicated for long-term administration, and they may cause local or, rarely, systemic adverse effects.[60] Patients or caregivers frequently admit to nonadherence due to worries about their safety. Oral antihistamines are recommended for control of pruritus.[60] Although sedating antihistamines may seem a sensible choice for this purpose, nighttime use of first-generation antihistamines has been shown to have a detrimental impact on next-day functioning[61]; therefore, nonsedating antihistamines are preferred overall. In severe cases, a short course of oral steroids (tapered over 2 to 3 weeks) can be tried.[25]

Two topical calcineurin inhibitors, tacrolimus and pimecrolimus, have been approved for use in patients with atopic dermatitis as young as 2 years of age. These nonsteroidal macrolactones interfere with transcription of inflammatory cytokines and may have other mechanisms of action as well.[60,62] They significantly reduce staphylococcal colonization of skin and control the symptoms of atopic dermatitis, reducing flare-ups and the need for steroid therapy.[62,63]

NEW AND FUTURE APPROACHES TO ALLERGY MANAGEMENT

Recent advances in the understanding of immune mechanisms, including mast cell activation, lymphocyte stimulation, inflammatory cell recruitment, and the actions of cytokines and chemokines, have provided new targets for the treatment of allergic diseases. For example, a monoclonal antibody directed against IgE has been shown to reduce serum IgE levels effectively and to reduce the symptoms of allergic rhinitis and allergic asthma. It has also been shown to increase the threshold of sensitivity to peanuts in allergic patients significantly, to a level that could protect against some unintended ingestions.[64] Other strategies being explored include inflammatory cytokines and their receptors and vaccination with immunoregulatory oligonucleotides.

CURRENT ISSUES IN ALLERGY MANAGEMENT

There are several issues that the clinician must consider in managing allergy in today's healthcare environment. Among them are the role of alternative medicine, the impact of adverse effects on adherence, and strategies for supporting long-term acceptance of treatment.

The Role of Complementary and Alternative Medicine

The use of complementary or alternative medicine (CAM), including a broad range of herbal and botanical agents, has burgeoned in the United States in recent years. Estimates are that in 1997, some 83 million people used alternative agents to treat their symptoms, spending in excess of $27 billion for these self-pay therapies—more than the out-of-pocket costs for all stays in American hospitals.[65] Allergy is second only to back pain as the most common chronic condition for which people seek alternative therapies.[66] In a 2001 survey of 300 adults with rhinosinusitis or asthma, 127 respondents (42%) reported using a complementary or alternative agent during the previous year; of these, 33 subjects (26%) were not using any prescription medication.[67]

Although there are some data to support the use of some alternative agents in the treatment of AR, well-controlled, rigorously designed research is scarce.[65,66] Despite the lack of evidence, many patients mistakenly believe that these agents are safe because they are derived from plants. In fact, the chemical composition of flowering and herbal plants is complex, and many are toxic.[66] Moreover, the manufacture of these agents is largely unregulated; there are no standards to ensure their potency or purity.[65] Patients who perceive benefits from using these agents are likely to continue using them and will distrust physicians who simply instruct them to discontinue use. Unless the CAM product is clearly dangerous, the healthcare provider should instead seek opportunities to initiate a nonjudgmental dialogue about it and provide balanced education and information.

CONCLUSION

Allergic diseases affect millions of Americans annually, and the number of sufferers grows with each passing year. Despite these enormous numbers, the time constraints of today's clinical practice limit the amount of attention that can be devoted to meticulous analysis of symptoms, repeated adjustments of therapy, and thorough patient education. However, given their extremely high prevalence, the profoundly adverse impact on QOL and functional capacity, and the potential for serious sequelae, allergic diseases must not be dismissed casually. Rather, they merit close clinical scrutiny and a multidisciplinary approach to prevention and treatment. Fortunately, recent advances in air-filtering technologies and food-labeling requirements allow many patients to avoid or reduce allergen exposure in ways they never could before. In addition, new and more potent drugs and delivery formulations are now available; but require thoughtful education of prescribers—with this information, physicians can now develop individualized treatment plans that are effective, safe, and acceptable to patients throughout the course of their disease.

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CURRENT TRENDS IN ALLERGIC REACTIONS: A MULTIDISCIPLINARY APPROACH TO PATIENT MANAGEMENT

CME Credit Information and Post Test

The estimated time to read the newsletter and complete the post test is 1 hour.

Release date: June 2003 — Expiration date: June 2004

PHYSICIANS

This activity has been jointly planned and implemented in accordance with the Essentials Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of National Jewish Medical and Research Center and IMED Communications. National Jewish Medical and Research Center is accredited by the ACCME to provide continuing medical education for physicians.

National Jewish Medical and Research Center designates this educational activity for up to 1 category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

Instructions:

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PHYSICIAN ASSISTANTS

This program has been reviewed and is approved for a maximum of 1 hour of clinical Category I (Preapproved) CME credit by the American Academy of Physician Assistants. Approval is valid for 1 year from the issue date of June 2003. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

Successful completion of the self-assessment is required to earn Category I (Preapproved) CME credit. Successful completion is defined as a cumulative score of at least 70% correct.

Instructions:

To receive CME credit, Physician Assistants should submit this post test online. You will get immediate feedback and can print your certificate of completion right away. (70% correct required for credit.) Sign onto the AAPA website at www.aapa.org and go to the CME services section. Click on the link to "Post-Tests Online."

POST TEST

1. In the allergic sensitization process, what becomes bound to high-affinity receptors on basophils and mast cells?
   a. T cells
   b. Antigen-specific IgE
   c. Tacrolimus
   d. B cells

2. The dramatic increase in incidence of latex allergy over the past decade or so is most likely related to which of the following developments?
   a. The increase in the volume of tropical fruits, such as passion fruit and bananas, into the United States
   b. The increase in the incidence of spina bifida
   c. The increased use of latex gloves
   d. The increased use of latex condoms

3. Which of the following is NOT among the most common causes of food allergy in adults?
   a. Peanuts
   b. Tree nuts
   c. Fish
   d. Milk

4. What are the 2 most common complaints of patients with allergic rhinoconjunctivitis?
   a. Ocular pain and photophobia
   b. Watery and itchy eyes
   c. Red and sore eyes
   d. Stinging and swelling of the eyes

5. The sedating effects of first-generation antihistamines are due to their:
   a. Lipophilicity
   b. Antiserotonin effects
   c. Anticholinergic effects
   d. All of the above

6. Rhinitis medicamentosa is a side effect of what type of AR therapy?
   a. Intranasal decongestants
   b. Oral corticosteroids
   c. Intranasal corticosteroids
   d. Mast cell stabilizers

7. IgE-mediated drug reactions typically manifest as:
   a. Immune hemolytic anemia
   b. Serum sickness or lupus syndromes
   c. Urticaria, pruritus, and/or angioedema
   d. Contact dermatitis

8. Potential triggers of atopic dermatitis include:
   a. Foods
   b. Aeroallergens such as dust mites
   c. Toxins secreted by *Staphylococcus aureus*
   d. All of the above

9. How should patients with AR be advised to use nasal steroids?
   a. As early as possible after the onset of symptoms
   b. On a regular basis, even when symptoms are not present
   c. One hour prior to anticipated exposure to allergens
   d. None of the above

10. Which symptoms of AR are mediated by histamine?
    a. Tickling and itching
    b. Sneezing and nose rubbing
    c. Postnasal drip and nasal congestion
    d. All of the above

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CURRENT TRENDS IN ALLERGIC REACTIONS:

A Multidisciplinary Approach to Patient Management Highlights Newsletter

Continuing Education Post Test

1.	O a.	O b.	O c.	O d.	6.	O a.	O b.	O c.	O d.
2.	O a.	O b.	O c.	O d.	7.	O a.	O b.	O c.	O d.
3.	O a.	O b.	O c.	O d.	8.	O a.	O b.	O c.	O d.
4.	O a.	O b.	O c.	O d.	9.	O a.	O b.	O c.	O d.
5.	O a.	O b.	O c.	O d.	10.	O a.	O b.	O c.	O d.

Program Evaluation

Your frank evaluation of this activity will be helpful in improving our continuing education programs. We hope this newsletter has provided information that will be useful in your practice. Please evaluate the newsletter by answering the following questions.

1. How would you rate:	Superior	Excellent	Good	Fair	Poor
a. Value of the topic	O	O	O	O	O
b. Relevance to your practice	O	O	O	O	O
c. Quality of information	O	O	O	O	O

2. Did this material succeed in meeting its educational objectives? O Yes O No
3. Will reading this newsletter change the way in which you treat patients? O Yes O No
4. Do you believe the newsletter contained pharmaceutical industry bias? O Yes O No
5. When information is presented by a federal healthcare agency (i.e. NIH, DHHS, CDC) does it increase the likelihood that you will read it?
   O Yes, definitely O Neutral O No, no change

6. How do you prefer to receive continuing medical education information?	Very Useful	Somewhat Useful	Don't Use
a. Newsletter	O	O	O
b. Monograph	O	O	O
c. Symposium/Conference	O	O	O
d. Journal Articles	O	O	O
e. Teleconference	O	O	O
f. CD-ROM/Audio and/or video	O	O	O
g. Internet	O	O	O

7. Actual amount of time I spent in this activity: [ ] . [ ][ ] Hours

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VOLUME 5 NO. 1

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